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**TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371**

U.S. APPLICATION NO. (If known, see 37  
CFR 1.5) (Not Yet Assigned - U.S. National  
Phase of Int'l PCT)  
**10/049776**

INTERNATIONAL APPLICATION  
NO. PCT/FR00/02329

INTERNATIONAL FILING DATE  
17 August 2000

PRIORITY DATE CLAIMED  
19 August 1999

**TITLE OF INVENTION: COMPOSITION FOR TOPICAL ADMINISTRATION, COMPRISING  
5-METHOXYPSORALEN**

**APPLICANT(S) FOR DO/EO/US** Jean-Jacques GOUPIL

Applicant herewith submits to the United States Designated/Elected Office(DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(I).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☐ have not been made and will not be made
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). (Unexecuted)
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11. to 16. below concern other document(s) or information included:**

11. ☐ An Information Disclosure Statement under 37 CFR 1.56, 1.97 and 1.98 with PTO Form 1449 attached;
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.  
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information:

PCT International Application Published Under the Patent Cooperation Treaty (Cover Page);  
PCT International Search Report (Form PCT/ISA/210);  
PCT Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).  
PCT Request (Form PCT/RO/101)

17. ☒ The following fees are submitted:

**BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):**

Search report has been prepared by the EPO or JPO ..... \$ 890.00  
 International preliminary examination fee paid to USPTO (37 CFR 1.482) \$  
 No international preliminary examination fee paid to USPTO (37 CFR 1.482  
 but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... \$  
 Neither international preliminary examination fee (37 CFR 1.482) nor  
 international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$  
 International preliminary examination fee paid to USPTO (37 CFR 1.482)  
 and all claims satisfied provision of PCT Article 33(2)-(4) ..... \$

**ENTER APPROPRIATE BASIC FEE AMOUNT = \$890.00**

Surcharge of \$130.00 for furnishing the oath or declaration later than  
☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).

\$130.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	14 -20 =	0	X \$18.00	\$0.00	
Independent Claims	1 - 3 =	0	X \$84.00	\$0.00	
Multiple dependent claims(s) (if applicable)			+ \$280.00	\$0.00	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>\$1,020.00</b>	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$510.00	
<b>SUBTOTAL =</b>				<b>\$510.00</b>	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$0.00	
<b>TOTAL NATIONAL FEE =</b>				<b>\$510.00</b>	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31).					
<b>\$ 40.00 per property +</b>				<b>\$</b>	
<b>TOTAL FEES ENCLOSED =</b>				<b>\$510.00</b>	
				Amount to be:	
				refunded	\$
				charged	\$

- a. ☒ A check in the amount of \$ 510.00 to cover the above fees is enclosed.  
 b. ☐ Please charge my Deposit Account No. 08-1650 in the amount of \$ \_\_\_\_\_ to cover the above fees. A duplicate copy of this sheet is enclosed.  
 c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 08-1650.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:  
 HENDERSON & STURM LLP  
 206 Sixth Avenue, Suite 1213  
 Des Moines, Iowa 50309-4076  
 Telephone: (515) 288-9589

*Michael O. Sturm*  
 Michael O. Sturm  
 Reg. No.: 26,078

Date: Feb. 19, 2002

10/049776  
PCT Rec'd 10 MAY 2002IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of )  
GOUPIL ) Art Unit :  
From PCT Appln FR00/02329 )  
Serial No. 10/049,776 )  
Filed: February 19, 2002 ) Examiner :

FOR : COMPOSITION FOR TOPICAL ADMINISTRATION COMPRISING  
5-METHOXYPYSORALEN

PRELIMINARY AMENDMENT

To the Honorable Commissioner of Patents and Trademarks  
Washington, D.C. 20231

Sir :

Before examination, kindly amend this application  
in accordance with the following particulars :

IN THE SPECIFICATION :

Please introduce the following titles in :

- Page 1, line 4 : FIELD OF THE INVENTION
- Page 1, line 11 : BACKGROUND OF THE INVENTION
- Page 3, line 32 : OBJECTS AND DESCRIPTION OF  
THE INVENTION

IN THE CLAIMS:

Please delete without prejudice claims 1-7 and 8 through 11, and substitute therefore new claims 12-25.

-- 12. A composition for topical administration, comprising 5-methoxypsoralen, the 5-MOP concentration in the composition being adjusted by adding a suitable amount of bergaptene-free natural citrus (bergamot) essence.

13. The composition of claim 12, wherein the 5-MOP concentration is 1 to 100 ppm.

14. The composition of claim 13, wherein the 5-MOP concentration is 1 to 60 ppm.

15. The composition of claim 12, wherein the 5-MOP concentration is 60 to 100 ppm.

16. The composition of claim 12, wherein the 5-MOP is introduced using pure natural citrus (bergamot) essence.

17. The composition of claim 12, in a form selected from the group consisting of a cream, an oil, a spray and a milk.

18. The composition of claim 12, which also comprises at least one ultraviolet screening agent.

19. The composition of claim 18, wherein the screening agent is an inorganic screening agent.

20. The composition of claim 19, wherein the screening agent is selected from the group consisting of titanium dioxide and zinc dioxide.

21. The composition of claim 18, wherein the screening agent is a chemical screening agent.

22. The composition of claim 21, wherein the screening agent is selected from the group consisting of ethylhexyl para-methoxycinnamate and 1,7,7-trimethyl-3-(4-methylbenzylidene)bicyclo[2.2.1]-hepta-2-one.

23. The composition of claim 18, which comprises 1 to 5% by weight of screening agent(s).

24. The composition of claim 12, which comprises no chemical screening agent.

25. The composition of claim 12, wherein its screening index is a maximum of 12, preferably a maximum of 10.--

Respectfully submitted,

May 10, 2002  
Date

Michael O. Sturm  
Michael O. Sturm  
Reg. No. 26, 078

HENDERSON & STURM LLP  
206 Sixth Avenue, Suite 1213  
Des Moines, Iowa 50309-4076

Telephone: 515-288-9589  
Telefax: 515-288-4860

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GOUPIL ) Art Unit :  
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Please delete without prejudice claims 1 to 11 and substitute therefor new claims 12 to 25 :

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23. The composition of claim 18, which comprises 1 to 5% by weight of screening agent(s).



24. The composition of claim 12, which comprises no chemical screening agent.

25. The composition of claim 12, wherein its screening index is a maximum of 12, preferably a maximum of 10.--

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Date                      Michael O. Sturm  
                                 Reg. No. 26,078

HENDERSON & STURM LLP  
206 Sixth Avenue, Suite 1213  
Des Moines, Iowa 50309-4076

Telephone: 515-288-9589  
Telefax: 515-288-4860

COMPOSITION FOR TOPICAL ADMINISTRATION, COMPRISING  
5-METHOXYPSORALEN

*Field of the Invention.*

✓ The present invention relates to a composition for  
5 topical administration, comprising 5-methoxypsoralen  
(bergaptene), and more particularly to a composition in  
which the 5-methoxypsoralen concentration is adjusted  
to the value selected by adding 5-methoxypsoralen and a  
suitable amount of bergaptene-free natural citrus  
10 (bergamot) essence.

*Background of the Invention*

In certain antison products, citrus (bergamot) essence  
is used, which makes it possible, under the action of  
ultraviolet rays, to increase the quality, rapidity and  
15 intensity of the production of melanin, a protective  
pigment, by the cells of the epidermis called  
melanocytes. The melanin is absorbed by other cells of  
the epidermis, keratinocytes, which migrate toward the  
surface of the epidermis during their lifetime. Natural  
20 tanning is the result of the presence of melanin at the  
surface.

This protective natural tanning phenomenon occurs  
naturally during exposure to sunlight, but it is  
25 reinforced when an individual applies to his or her  
skin an antison product containing natural citrus  
(bergamot) essence.

Natural citrus (bergamot) essence extracted in  
30 particular from *Citrus bergamia* in particular contains  
5-methoxypsoralen, also called 5-MOP or bergaptene.

It has been possible to demonstrate that natural citrus  
(bergamot) essence not only has a positive beneficial  
35 action on cells, reinforcing the natural reaction of  
the body, i.e. protective natural tanning, but that it  
also has a preventive effect, through the protection of  
the DNA of skin cells.

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The 5-MOP concentration of natural citrus (bergamot) essence is not constant and may vary with in the range from 1 to 5%, most commonly no more than 3%, depending in particular on the citrus species, on the seasons, on the soil, on the climate and on the time of the harvest. This concentration may be measured in particular by gas-phase chromatography.

5-MOP may also be added to a composition in the form of a pure product.

The amount of citrus (bergamot) essence or of 5-MOP in an antisen product has been the subject of regulations in many countries. In the United States for example, according to the Consumer Product Safety Commission, a concentration of 2% of pure natural bergamot essence may not currently be exceeded in a cosmetic product. Moreover, the European Commission has excessively limited the 5-MOP concentration in an antisen product to 1 ppm. This maximum limit, which may be removed or modified in the future, does not apply to medicinal products, which must be the subject of a marketing authorization.

In addition, the great effectiveness of natural citrus (bergamot) essence must be strictly controlled.

It is therefore important to control with precision the amount of natural citrus (bergamot) essence and/or of 5-MOP present in an antisen composition.

In the prior art, the desired amount of 5-MOP could be obtained by varying the amount of citrus (bergamot) essence or the amount of pure 5-MOP in the product.

French patent FR 2 360 301 thus describes an antisen product in which the 5-MOP content comes from citrus (bergamot) essence to which pure 5-MOP is added in

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order to obtain a high 5-MOP concentration without using too great an amount of citrus (bergamot) essence.

However, the Applicant has noted that such products are  
5 not entirely satisfactory.

Specifically, the only way to obtain low concentrations of 5-MOP in a composition of the prior art is to use small amounts of pure 5-MOP or of citrus (bergamot)  
10 essence.

Now, natural citrus (bergamot) essence contains components other than 5-MOP, and in particular other chromophores such as bergamotin or citropten. If a  
15 small amount of citrus essence is used in order to obtain a low 5-MOP concentration in the composition, the benefit of the presence of the other components of this essence, such as bergamotin, is simultaneously lost.

20 If only pure 5-MOP is used, it is obvious that the other components of the natural citrus (bergamot) essence will also be absent.

25 To its credit, the Applicant has succeeded in developing a composition for topical administration, comprising 5-MOP at a concentration possibly attaining very low values without, however, losing the benefit of the presence of the other components of the natural  
30 citrus (bergamot) essence, such as the other chromophores.

### *Objects and Description of the Invention*

A subject of the present invention is therefore a composition for topical administration, comprising 5-  
35 MOP, in which the 5-MOP concentration is adjusted by adding 5-MOP and a suitable amount of bergaptene-free natural citrus (bergamot) essence.

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The natural citrus (bergamot) essence is in particular extracted from *Citrus bergamia*.

5 The 5-MOP will preferably be introduced into the composition using pure natural citrus (bergamot) essence.

The term "pure citrus essence" means that the essence is not bergaptene-free.

10

The 5-MOP may also be added in the form of pure 5-MOP.

15 The addition of bergaptene-free natural citrus (bergamot) essence makes it possible to dilute the 5-MOP present in the pure natural citrus (bergamot) essence, or the pure 5-MOP. It is thus possible to obtain, depending on the mixture selected, a 5-MOP concentration in the composition of 1 ppm to 100 ppm, preferably of 1 ppm to 60 ppm. All intermediate values  
20 are possible, for example 15 ppm, 30 ppm or 45 ppm.

When the 5-MOP is introduced in the form of pure citrus essence, the total concentration of citrus essence (pure and bergaptene-free) may be kept constant while  
25 at the same time varying the relative proportions of pure essence and of bergaptene-free essence so as to vary the amount of 5-MOP in the composition. Preferably, the pure citrus (bergamot) essence content in the composition is a maximum of 2% by weight, in  
30 order to respect the American regulations.

Thus, if an amount  $x$  of pure natural citrus essence gives a concentration  $y$  of 5-MOP in the composition, then an amount  $x/2$  of pure natural citrus essence and  
35 an amount  $x/2$  of bergaptene-free natural citrus essence will be needed in order to obtain a concentration  $y/2$  of 5-MOP in the composition, the other components (in particular the chromophores) remaining unchanged.

By way of example, an amount of 2% by weight of pure natural citrus (bergamot) essence in a composition corresponds to a 5-MOP concentration in the composition  
5 of approximately 60 ppm.

The bergaptene-free natural citrus (bergamot) essence may be obtained by distilling the natural citrus essence.

10

The composition according to the invention is administered topically. It therefore comprises, in suitable proportions, the excipient(s) suitable for such an application, for example peanut oil, water,  
15 ethyl cocoate, octyl cocoate, polyoxyethylenated hydrogenated castor oil and liquid paraffin. Such excipients are known to those skilled in the art. The composition may in particular be in the form of a milk, a cream, a spray or an oil.

20

The composition also preferably comprises at least one ultraviolet screening agent, which may be a chemical screening agent or an inorganic screening agent, which may or may not be micronized, but preferentially an  
25 inorganic screening agent. Preferably, the composition does not comprise any chemical screening agent.

The chemical screening agents which may be used are, for example, ethylhexyl para-methoxycinnamate and  
30 1,7,7-trimethyl-3-(4-methylbenzylidene)bicyclo[2.2.1]-heptan-2-one.

The inorganic screening agents which may be used are, for example, titanium dioxide and zinc dioxide.

35

The screening coefficient or index of the composition depends on the concentration of screening agent(s) in said composition. Preferably, from 1 to 5% by weight of

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screening agent(s) is added, in order to obtain a screening index which preferably does not exceed 12, even more preferably does not exceed 10. In fact, too high a screening index may prevent the skin from tanning and therefore from naturally protecting itself against sunlight. It is therefore preferable to maintain a screening index at a maximum of 12, or even at a maximum of 10, for example from 2 to 10, in order to preserve and not to hinder the natural protection of the skin against sunlight, i.e. tanning. It is understood, however, that the screening coefficient may be increased if desired. The suitable amount of screening agent(s) will be determined by those skilled in the art depending on the desired screening effect.

The composition according to the invention may also comprise other components, such as, for example, conventional emollients or vitamins.

#### Examples

The following compositions are given by way of examples, and should in no way be considered to limit the scope of the invention. All the figures are given in grams per 100 g of composition. The screening indices obtained range from 3 to 10.

#### - Compositions 1 to 3:

These are compositions which are in the form of an oil, and in which the 5-MOP content is 60 ppm (composition 1), 30 ppm (composition 2) and 1 ppm (composition 3).

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Table 1:

Component	1	2	3
Peanut oil	66.99	66.59	65.59
Ethyl cocoate	25	25	25
Isononyl isononanoate	5	5	5
Titanium dioxide	0.5	1	2
Pure citrus (bergamot) essence	2	1	0.03
Bergaptene-free citrus (bergamot) essence	0.1	1	1.97
Tocopherol acetate	0.25	0.25	0.25
Butylated hydroxytoluene	0.08	0.08	0.08
Vitamin A palmitate	0.075	0.075	0.075
Butylated hydroxyanisole	0.005	0.005	0.005

- Compositions 4 to 6:

- 5 These are compositions which are in the form of a milk, and in which the bergaptene content is 60 ppm (composition 4), 30 ppm (composition 5) and 1 ppm (composition 6).

Table 2:

Component	4	5	6
Water	59.615	59.215	58.215
Liquid paraffin	7.5	7.5	7.5
Octyl cocoate	6.0	6.0	6.0
Polyoxyethylenated (7 moles) hydrogenated castor oil	6.0	6.0	6.0
Isononyl isononanoate	5.0	5.0	5.0
Peanut oil	3.0	3.0	3.0
Polypropylene glycol (15 moles) stearyl ether	3.0	3.0	3.0
Glyceryl/sorbitol oleate/hydroxystearate	3.0	3.0	3.0
Glycerol	3.0	3.0	3.0
Titanium dioxide	0.5	1	2



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Pure citrus (bergamot) essence	2	1	0.03
Bergaptene-free citrus (bergamot) essence	0.1	1	1.97
Glyceryl hydroxystearate	0.5	0.5	0.5
Tocopherol acetate	0.25	0.25	0.25
Imidazolidinyl urea	0.2	0.2	0.2
Sodium methyl parahydroxybenzoate	0.2	0.2	0.2
Vitamin A palmitate	0.075	0.075	0.075
Butylated hydroxyanisole	0.04	0.04	0.04
Butylated hydroxytoluene	0.02	0.02	0.02

A composition according to the invention may therefore be used in the field of antisen products, as detailed above. Other topical applications can be envisaged, in particular in the medical field. In this case, the 5-MOP concentration will generally be greater than the concentration of the cosmetic applications, for example between 60 and 100 ppm. In particular, a composition according to the invention may be used in PUVA therapy, i.e. in the treatment of various types of dermatosis, such as psoriasis. The composition according to the invention may also be used in the hair-related domain, in particular to avoid or delay hair loss or the appearance of white hairs, and to promote regrowth.

CLAIMS

1. A composition for topical administration, comprising 5-methoxypsoralen, the 5-MOP concentration  
5 in the composition being adjusted by adding a suitable amount of bergaptene-free natural citrus (bergamot) essence.
2. The composition as claimed in claim 1,  
10 characterized in that the 5-MOP concentration is 1 to 100 ppm, preferably 1 to 60 ppm.
3. The composition as claimed in claim 1,  
15 characterized in that the 5-MOP concentration is 60 to 100 ppm.
4. The composition as claimed in any one of claims 1 to 3, characterized in that the 5-MOP is introduced using pure natural citrus (bergamot) essence.  
20
5. The composition as claimed in any one of claims 1 to 4, characterized in that it is in the form of a cream, an oil, a spray or a milk.
- 25 6. The composition as claimed in any one of claims 1 to 5, characterized in that it also comprises at least one ultraviolet screening agent.
7. The composition as claimed in claim 6,  
30 characterized in that the screening agent is an inorganic screening agent, preferably chosen from titanium dioxide and zinc dioxide.
8. The composition as claimed in either of claims 6  
35 and 7, characterized in that it comprises 1 to 5% by weight of screening agent(s).

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9. The composition as claimed in any one of claims 1 to 8, characterized in that it does not comprise any chemical screening agent.
- 5 10. The composition as claimed in any one of claims 1 to 9, characterized in that its screening index is a maximum of 12, preferably a maximum of 10.

**AMENDED CLAIMS**

[Received by the International Bureau on January 26, 2001 (26.01.01); original claims 8 to 10 replaced with new claims 8 to 11; other claims unchanged (1 page)]

5

8. The composition as claimed in claim 6, characterized in that the screening agent is a chemical screening agent, in particular a screening agent chosen  
10 from ethylhexyl para-methoxycinnamate and 1,7,7-trimethyl-3-(4-methylbenzylidene)bicyclo[2.2.1] hepta-2-one.

9. The composition as claimed in any one of claims 6  
15 to 8, characterized in that it comprises 1 to 5% by weight of screening agent(s).

10. The composition as claimed in any one of claims 1  
20 to 9, characterized in that it does not comprise any chemical screening agent.

11. The composition as claimed in any one of claims 1 to 10, characterized in that its screening index is a maximum of 12, preferably a maximum of 10.

WO 01/13873

PCT/FR00/02329

- 1 -

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Natural citrus (bergamot) essence extracted in  
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The 5-MOP concentration of natural citrus (bergamot) essence is not constant and may vary within the range from 1 to 5%, most commonly no more than 3%, depending in particular on the citrus species, on the seasons, on the soil, on the climate and on the time of the harvest. This concentration may be measured in particular by gas-phase chromatography.

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In addition, the great effectiveness of natural citrus (bergamot) essence must be strictly controlled.

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In the prior art, the desired amount of 5-MOP could be obtained by varying the amount of citrus (bergamot) essence or the amount of pure 5-MOP in the product.

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However, the Applicant has noted that such products are  
5 not entirely satisfactory.

Specifically, the only way to obtain low concentrations of 5-MOP in a composition of the prior art is to use small amounts of pure 5-MOP or of citrus (bergamot)  
10 essence.

Now, natural citrus (bergamot) essence contains components other than 5-MOP, and in particular other chromophores such as bergamotin or citropten. If a  
15 small amount of citrus essence is used in order to obtain a low 5-MOP concentration in the composition, the benefit of the presence of the other components of this essence, such as bergamotin, is simultaneously lost.

20 If only pure 5-MOP is used, it is obvious that the other components of the natural citrus (bergamot) essence will also be absent.

25 To its credit, the Applicant has succeeded in developing a composition for topical administration, comprising 5-MOP at a concentration possibly attaining very low values without, however, losing the benefit of the presence of the other components of the natural  
30 citrus (bergamot) essence, such as the other chromophores.

A subject of the present invention is therefore a composition for topical administration, comprising 5-  
35 MOP, in which the 5-MOP concentration is adjusted by adding 5-MOP and a suitable amount of bergaptene-free natural citrus (bergamot) essence.

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The natural citrus (bergamot) essence is in particular extracted from *Citrus bergamia*.

5 The 5-MOP will preferably be introduced into the composition using pure natural citrus (bergamot) essence.

10 The term "pure citrus essence" means that the essence is not bergaptene-free.

The 5-MOP may also be added in the form of pure 5-MOP.

15 The addition of bergaptene-free natural citrus (bergamot) essence makes it possible to dilute the 5-MOP present in the pure natural citrus (bergamot) essence, or the pure 5-MOP. It is thus possible to obtain, depending on the mixture selected, a 5-MOP concentration in the composition of 1 ppm to 100 ppm, preferably of 1 ppm to 60 ppm. All intermediate values  
20 are possible, for example 15 ppm, 30 ppm or 45 ppm.

When the 5-MOP is introduced in the form of pure citrus essence, the total concentration of citrus essence (pure and bergaptene-free) may be kept constant while  
25 at the same time varying the relative proportions of pure essence and of bergaptene-free essence so as to vary the amount of 5-MOP in the composition. Preferably, the pure citrus (bergamot) essence content in the composition is a maximum of 2% by weight, in  
30 order to respect the American regulations.

Thus, if an amount  $x$  of pure natural citrus essence gives a concentration  $y$  of 5-MOP in the composition, then an amount  $x/2$  of pure natural citrus essence and  
35 an amount  $x/2$  of bergaptene-free natural citrus essence will be needed in order to obtain a concentration  $y/2$  of 5-MOP in the composition, the other components (in particular the chromophores) remaining unchanged.



- 5 -

By way of example, an amount of 2% by weight of pure natural citrus (bergamot) essence in a composition corresponds to a 5-MOP concentration in the composition of approximately 60 ppm.

The bergaptene-free natural citrus (bergamot) essence may be obtained by distilling the natural citrus essence.

10

The composition according to the invention is administered topically. It therefore comprises, in suitable proportions, the excipient(s) suitable for such an application, for example peanut oil, water, ethyl cocoate, octyl cocoate, polyoxyethylenated hydrogenated castor oil and liquid paraffin. Such excipients are known to those skilled in the art. The composition may in particular be in the form of a milk, a cream, a spray or an oil.

20

The composition also preferably comprises at least one ultraviolet screening agent, which may be a chemical screening agent or an inorganic screening agent, which may or may not be micronized, but preferentially an inorganic screening agent. Preferably, the composition does not comprise any chemical screening agent.

The chemical screening agents which may be used are, for example, ethylhexyl para-methoxycinnamate and 1,7,7-trimethyl-3-(4-methylbenzylidene)bicyclo[2.2.1]-heptan-2-one.

The inorganic screening agents which may be used are, for example, titanium dioxide and zinc dioxide.

35

The screening coefficient or index of the composition depends on the concentration of screening agent(s) in said composition. Preferably, from 1 to 5% by weight of

- 6 -

screening agent(s) is added, in order to obtain a screening index which preferably does not exceed 12, even more preferably does not exceed 10. In fact, too high a screening index may prevent the skin from tanning and therefore from naturally protecting itself against sunlight. It is therefore preferable to maintain a screening index at a maximum of 12, or even at a maximum of 10, for example from 2 to 10, in order to preserve and not to hinder the natural protection of the skin against sunlight, i.e. tanning. It is understood, however, that the screening coefficient may be increased if desired. The suitable amount of screening agent(s) will be determined by those skilled in the art depending on the desired screening effect.

The composition according to the invention may also comprise other components, such as, for example, conventional emollients or vitamins.

#### 20 Examples

The following compositions are given by way of examples, and should in no way be considered to limit the scope of the invention. All the figures are given in grams per 100 g of composition. The screening indices obtained range from 3 to 10.

#### - Compositions 1 to 3:

These are compositions which are in the form of an oil, and in which the 5-MOP content is 60 ppm (composition 1), 30 ppm (composition 2) and 1 ppm (composition 3).

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Table 1:

Component	1	2	3
Peanut oil	66.99	66.59	65.59
Ethyl cocoate	25	25	25
Isononyl isononanoate	5	5	5
Titanium dioxide	0.5	1	2
Pure citrus (bergamot) essence	2	1	0.03
Bergaptene-free citrus (bergamot) essence	0.1	1	1.97
Tocopherol acetate	0.25	0.25	0.25
Butylated hydroxytoluene	0.08	0.08	0.08
Vitamin A palmitate	0.075	0.075	0.075
Butylated hydroxyanisole	0.005	0.005	0.005

- Compositions 4 to 6:

These are compositions which are in the form of a milk,  
 5 and in which the bergaptene content is 60 ppm (composition 4), 30 ppm (composition 5) and 1 ppm (composition 6).

Table 2:

Component	4	5	6
Water	59.615	59.215	58.215
Liquid paraffin	7.5	7.5	7.5
Octyl cocoate	6.0	6.0	6.0
Polyoxyethylenated (7 moles) hydrogenated castor oil	6.0	6.0	6.0
Isononyl isononanoate	5.0	5.0	5.0
Peanut oil	3.0	3.0	3.0
Polypropylene glycol (15 moles) stearyl ether	3.0	3.0	3.0
Glyceryl/sorbitol oleate/hydroxystearate	3.0	3.0	3.0
Glycerol	3.0	3.0	3.0
Titanium dioxide	0.5	1	2

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Pure citrus (bergamot) essence	2	1	0.03
Bergaptene-free citrus (bergamot) essence	0.1	1	1.97
Glyceryl hydroxystearate	0.5	0.5	0.5
Tocopherol acetate	0.25	0.25	0.25
Imidazolidinyl urea	0.2	0.2	0.2
Sodium methyl parahydroxybenzoate	0.2	0.2	0.2
Vitamin A palmitate	0.075	0.075	0.075
Butylated hydroxyanisole	0.04	0.04	0.04
Butylated hydroxytoluene	0.02	0.02	0.02

A composition according to the invention may therefore be used in the field of antisen products, as detailed above. Other topical applications can be envisaged, in particular in the medical field. In this case, the 5-MOP concentration will generally be greater than the concentration of the cosmetic applications, for example between 60 and 100 ppm. In particular, a composition according to the invention may be used in PUVA therapy, i.e. in the treatment of various types of dermatosis, such as psoriasis. The composition according to the invention may also be used in the hair-related domain, in particular to avoid or delay hair loss or the appearance of white hairs, and to promote regrowth.

CLAIMS

1. A composition for topical administration, comprising 5-methoxypsoralen, the 5-MOP concentration  
5 in the composition being adjusted by adding a suitable amount of bergaptene-free natural citrus (bergamot) essence.
2. The composition as claimed in claim 1,  
10 characterized in that the 5-MOP concentration is 1 to 100 ppm, preferably 1 to 60 ppm.
3. The composition as claimed in claim 1,  
15 characterized in that the 5-MOP concentration is 60 to 100 ppm.
4. The composition as claimed in any one of claims 1 to 3, characterized in that the 5-MOP is introduced using pure natural citrus (bergamot) essence.  
20
5. The composition as claimed in any one of claims 1 to 4, characterized in that it is in the form of a cream, an oil, a spray or a milk.
- 25 6. The composition as claimed in any one of claims 1 to 5, characterized in that it also comprises at least one ultraviolet screening agent.
7. The composition as claimed in claim 6,  
30 characterized in that the screening agent is an inorganic screening agent, preferably chosen from titanium dioxide and zinc dioxide.
8. The composition as claimed in either of claims 6  
35 and 7, characterized in that it comprises 1 to 5% by weight of screening agent(s).

- 10 -

9. The composition as claimed in any one of claims 1 to 8, characterized in that it does not comprise any chemical screening agent.

- 5 10. The composition as claimed in any one of claims 1 to 9, characterized in that its screening index is a maximum of 12, preferably a maximum of 10.

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(71) Déposant et

(72) Inventeur: GOUPIL, Jean-Jacques [FR/FR]; 96, route  
de Versailles, F-78460 Chevreuse (FR).

(74) Mandataires: VERCAEMER, Laurence etc.; Cabinet  
Plasseraud, 84, rue d'Amsterdam, F-75440 Paris Cedex 09  
(FR).

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(54) Title: COMPOSITION FOR TOPICAL ADMINISTRATION COMPRISING 5-METHOXYPORALEN

(54) Titre: COMPOSITION POUR ADMINISTRATION TOPIQUE COMPRENANT DU 5-METHOXYPORALENE

(57) Abstract: The invention concerns a composition for topical administration comprising 5-MOP (bergaptene), whereof the 5-MOP concentration is adjusted to the value selected by the addition of 5-MOP, preferably using pure natural citrus (bergamot) essence, and of an appropriate amount of natural bergaptene-free citrus (bergamot) essence. Depending on the amount selected, the composition will have a 5-MOP concentration ranging between 1 ppm and 100 ppm, preferably between 1 ppm and 60 ppm for cosmetic use, or 60 to 100 ppm for therapeutic use. The invention is particular useful in the field of cosmetics, solar protection products, hair care products and for therapeutic purposes.

(57) Abrégé: L'invention a pour objet une composition pour administration topique comprenant du 5-MOP (bergaptène), dont la concentration en 5-MOP est ajustée à la valeur choisie grâce à l'adjonction de 5-MOP, de préférence au moyen d'essence de citrus (bergamote) naturelle pure, et d'une quantité appropriée d'essence de citrus (bergamote) naturelle débergapténée. En fonction de la quantité choisie, on obtiendra une concentration en 5-MOP dans la composition de 1 ppm à 100 ppm, de préférence de 1 ppm à 60 ppm dans le domaine cosmétique, ou de 60 à 100 ppm en thérapeutique. Application en particulier au domaine cosmétique, des produits solaires, des produits capillaires et en thérapeutique.

WO 01/13873 A1

PTO/SB/09 (10-92)

**VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS  
(37 CFR 1.9(f) & 1.27(b))--INDEPENDENT INVENTOR**

Docket Number (Optional)

Applicant or Patentee: GOUPIL Jean-Jacques

Serial or Patent No.: \_\_\_\_\_

Filed or Issued: \_\_\_\_\_

Title: COMPOSITION POUR ADMINISTRATION TOPIQUE COMPRENANT DU 5-METHOXYPSORALENE  
X COMPOSITION FOR TOPICAL ADMINISTRATION COMPRISING 5-METHOXYPSORALENE

As a below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees to the Patent and Trademark Office described in:

- ☐ the specification filed herewith with title as listed above.  
☒ the application identified above.  
☐ the patent identified above.

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

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- ☐ No such person, concern, or organization exists.  
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Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

GOUPIL Jean-Jacques  
NAME OF INVENTORGoupil  
Signature of inventor

Date

NAME OF INVENTOR

Signature of inventor

Date

Goupil Jean-Jacques  
NAME OF INVENTORGoupil  
Signature of inventorDate 25.2.02.



c:\form\2\declarat.pct

## COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

Docket No. \_\_\_\_\_

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled COMPOSITION FOR TOPICAL ADMINISTRATION COMPRISING 5-METHOXYPSORALEN the specification of which(check) ☒ is attached hereto.☐ was filed on \_\_\_\_\_ as Application Serial No. \_\_\_\_\_  
and was amended on \_\_\_\_\_ (if applicable).☐ was filed as PCT international application Number \_\_\_\_\_ on \_\_\_\_\_  
and was amended under PCT Article 19 on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information known to me to be material to patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application (s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application (s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is now claimed:

Prior Foreign Application(s)	FRANCE	19/08/1999	Priority Claimed
99 10632			X
(Number)	(Country)	(Day/Month/Year Filed)	Yes No
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(Number)	(Country)	(Day/Month/Year Filed)	Yes No
_____	_____	_____	Yes No
(Number)	(Country)	(Day/Month/Year Filed)	Yes No
_____	_____	_____	Yes No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

PCT FR00/02329	17/08/2000	
(Application Serial No.)	(Filing Date)	(Status-patented, pending, abandoned)
_____	_____	_____
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I hereby appoint the following attorney(s) and/or agents(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: H. Robert Henderson, Reg. No. 18,486; Michael O. Sturm, Reg. No. 26,078; John E. Cepican, Reg. No. 26,851; Richard L. Fix, Reg. No. 28,297; William H. Wright, Reg. No. 26,424; Martin G. Mullen, Reg. No. 28,574; Daniel B. Greenwood, Reg. No. 35,885; and Curtis A. Bell, Reg. No. 36,742.

Address all telephone calls to Martin G. Mullen telephone no. 202/296-3854  
Address all correspondence to: HENDERSON & STURM telefax no. 202/223-9606Suite 1020  
1301 Pennsylvania Avenue, N.W.  
Washington, DC 20004-1707

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Jean-Jacques GOURIL  
 Inventor's signature [Signature]  
 Date 25 03 2000  
 Residence 78460 CHEVREUSE (FRANCE)  
 Citizenship FRENCH  
 Post Office Address 96, route de Versailles 78460 CHEVREUSE (FRANCE)

Full name of second joint inventor, if any \_\_\_\_\_  
 Second Inventor's signature \_\_\_\_\_  
 Date \_\_\_\_\_  
 Residence \_\_\_\_\_  
 Citizenship \_\_\_\_\_  
 Post Office Address \_\_\_\_\_

Full name of third joint inventor, if any \_\_\_\_\_  
 Third Inventor's signature \_\_\_\_\_  
 Date \_\_\_\_\_  
 Residence \_\_\_\_\_  
 Citizenship \_\_\_\_\_  
 Post Office Address \_\_\_\_\_